Research

EasiVits – Acceptability and Tolerance Study

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EasiVits – Acceptability and Tolerance

1 INTRODUCTION

In order to achieve metabolic stability, dietary treatment of inborn errors of metabolism (IEM) may require restriction of protein (e.g. phenylketonuria, tyrosinaemia, homocystinuria, organic acidaemias, maple syrup urine disease (MSUD), urea cycle disorders), fat (e.g. fatty acid oxidation disorders) or carbohydrate (e.g. glycogen storage disease). Manipulation of dietary intake potentially reduces micronutrient status, and provision of a comprehensive vitamin and mineral supplement may become an essential adjunct to dietary treatment (Robert et al 2013; Daly et al 2016; Daly et al 2015).

Paediatric Seravit and Frutivits are vitamin and mineral supplements that are currently available on prescription. Paediatric Seravit is designed for children between 1-3 years of age but has high amounts of added carbohydrate, restricting its use for patients with IEM with restricted carbohydrate intake. Fruitivits is designed for children over the age of 3 years and is orange flavoured, restricting patient's choice, potentially leading to poor adherence and taste fatigue.

Previous studies show that despite improvements in some nutritional markers using the currently available vitamin and mineral supplements, overall use of the vitamin and mineral supplements was less than prescribed and alternatives are needed to guarantee delivery of micronutrients in children at risk of deficiencies as a result of an essential manipulation of diet in inborn disorders of metabolism (Daly et al, 2016). Whilst condition specific formula for IEM often contains added micronutrients, there are global concerns about over- and under-supplementation and the impact on palatability (Evans et al, 2025). Consequently, some health professionals advocate the availability of unfortified products to enable individualised tailoring of micronutrient intake using a separate vitamin and mineral supplement (Evans et al, 2025). Furthermore, with the advent of pharmacological treatments for some IEM, there is evidence that cessation of specialist formula without significant changes to

dietary food intake, commonly leads to deficiencies in several micronutrients (Brantley et al 2018; Thiele et al, 2013).

EasiVits are new vitamin and mineral supplements which contain minimal carbohydrate and are unflavoured. This allows them to be used in carbohydrate restricted IEMs, and patients can also add their preferred flavours via permitted fruit cordials or drinks in order to potentially improve adherence and prevent taste fatigue.

2 STUDY OBJECTIVES

2.1 Primary study objective

- To evaluate the acceptability of EasiVits for use in the dietary management of children with IEM over the age of 1 year with regard to product tolerance and adherence.

3 STUDY PARAMETERS

3.1 Primary study parameters

- Qualitative assessments from subject questionnaires that allow evaluation of the acceptability, tolerance and ease of use in administering the EasiVits vitamin and mineral supplement.
- The collection of daily data about the gastro-intestinal tolerance of the EasiVits vitamin and mineral supplement compared with the usual vitamin and mineral supplements.
- Collection of daily data about adherence with the study products (actual versus prescribed intake).
- Patient weight and height will be recorded at the study start and end.

4 STUDY DESIGN

4.1 Study design

This is a prospective, observational open label research study in 30 children with IEM (15 aged 1-3y and 15 aged 3-16 years). Subjects who are currently taking vitamin and mineral supplements for IEM will be recruited for a 7-day trial of the new EasiVits vitamin and mineral supplements, to evaluate the tolerability and acceptability of the study products compared with their usual products. Study subjects will replace their usual daily dose of vitamin and mineral supplement with the equivalent amount of the new EasiVits vitamin and mineral supplement for 7 days. The outcome of this assessment will be used in a submission to regulatory authorities to allow the study products to be reimbursable on prescription in the UK.

Subjects will be asked to take the new EasiVits vitamin and mineral supplement for 7 days. During this time, caregivers will be asked to complete a daily questionnaire recording information on:

- Usage and adherence
- Ease of use and any issues with administration
- Any gastro-intestinal side effects

The questions should take a maximum of 5-10 minutes to complete each day. Additional questions will also be completed at the beginning and end of the study that will consider opinions about product taste, appearance, smell, presentation and packaging of the product; ease of administration; how the new EasiVits vitamin and mineral supplement is taken; and any other problems or symptoms.

NeoteriQ Ltd. will supply the new EasiVits vitamin and mineral supplement for participants free of charge.

5 SUBJECTS

5.1 Study population

30 children, diagnosed with IEM who currently take a vitamin and mineral supplement will be recruited from one specialist IMD centre (e.g. urea cycle disorders – Agininosuccinic Aciduria (ASA), Hyperornithinemia-hyperammonemia-homocitrullinuria syndrome **(**HHH), Ornithine transcarbamylase deficiency (OTC), Citrin deficiency; Organic acidaemias - methylmalonic

acidaemia (MMA), propionic acidaemia (PA); glycogen storage disease).

5.2 Inclusion criteria

1. Male and female IEM patients ages 1-16 years.
2. Patients diagnosed with an IEM.
3. Taking vitamin and mineral supplements for IEM and willing to take the new supplements for 7 days.
4. Absence of comorbidities.
5. Adherence with dietary management and vitamin and mineral supplements.
6. Able to understand and comply with the requirements of the investigation and sign the Informed Consent Form/Assent form.

5.3 Exclusion criteria

1. Age <1 years old.
2. Patients with comorbidities.
3. Any moderate to severe acute illness which in the opinion of the Investigator would interfere with the study procedures or study outcome.
4. History of poor co-operation, non-adherence with dietary management, or poor adherence to investigation procedures.
5. Participation in any other studies involving investigational or marketed products concomitantly or within two weeks prior to entry into the study.

5.4 Subject recruitment

30 children with IEM will be recruited. When an appropriate subject has been identified, they and their parents/caregivers will be sent a study information sheet via the post. They will be invited to request further information about the study if they wish by contacting the Dietitian. The Dietitian will explain the study in more detail either by telephone or via a face-to-face consultation in a convenient location/preferred venue for the participant and their parent/caregiver. Recruitment of each patient will be by written informed consent, which will be completed by the parents/primary caregivers and taken by the Dietitian. Children will also complete an assent/consent form. Reimbursement will be offered for any travel expenses incurred for any visits to the hospital that are

over and above normal/routine visits.

5.5 Concomitant medications / treatments during the study

Any medications taken during the study will be documented (also see exclusion criteria).

6 STUDY DESCRIPTION

6.1 Study description

Subjects who currently take vitamin and mineral supplements will be recruited. Subjects will replace their daily dose of vitamin and mineral supplements with an equivalent amount of the study product for 7 days. Daily acceptability and tolerance questionnaires will record information on ease of preparation and administration; how it is taken; and any problems or gastro-intestinal effects. Additional questions at the beginning and end of the study will record information on taste, appearance, smell, presentation and packaging of the study products compared with the usual vitamin and mineral supplements. Weight and height will also be recorded at the beginning and end of the study.

6.2 Study sponsor, funding and investigators

The metabolic dietitians at Birmingham Children's Hospital will be organising the study under the supervision of Chief Investigator Professor Anita MacDonald, with funding and sponsorship from NeoteriQ Ltd, a company producing nutritional products for inherited metabolic disorders. Study participants will be recruited from Birmingham Children's Hospital.

7 STUDY PROCEDURES AND ASSESSMENTS

7.1 Study procedures

Acceptability and tolerance questionnaire:

The primary caregiver will complete a questionnaire at the beginning and end of the study and on each day of the study whilst their child consumes the new EasiVits vitamin and mineral supplement. This will assess daily intake of the new EasiVits vitamin and mineral supplement, and any side

effects associated with taking the new products. This information will contribute to a submission to regulatory authorities.

Supplement administration

A record will be kept daily of vitamin and mineral supplement intake, including when and how taken.

Weight and height

Weight and height will be recorded at the beginning and end of the study to monitor growth.

Adherence:

Prescription details, amendments and intakes will also be recorded by the dietitian.

Concomitant medication:

All concomitant medications taken during the study will be recorded in the case record file (CRF) with indication, dose information, and dates of administration. Permitted study medications will be those that in the opinion of the Investigator do not affect or interfere with the study procedures or outcomes.

8 STUDY PRODUCT

8.1 Description of study products

EasiVits are an unflavoured, unsweetened, and low carbohydrate, powdered blend of vitamins, minerals and trace elements. Designed for use in the dietary management of conditions requiring restricted therapeutic diets or unable to meet vitamin and mineral requirements from regular dietary intake in patients from the age of 1 year old.

UNO EasiVits is designed for patients between 1-3 years of age.
DUO EasiVits is designed for patients between 3-16 years of age.

For further details on the products, please see the product specification in Appendix 1.

8.2 Product administration and dosage

The dietitian will determine the recommended intake of the study product based on the amount of vitamins and minerals in the patient's current vitamin and mineral supplements. EasiVits is mixed with water and consumed immediately.

UNO EasiVits - mixed with a minimum of 30g of water.
DUO EasiVits - mixed with a minimum of 60g of water.

8.3 Preparation, packaging, labelling and storage

The study products are presented in 3g (UNO) or 5g (DUO) sachets. Store below 25ºC. Sachets are designed for single use and once opened should be used immediately. Any unused powder in an open sachet should be stored in an airtight container or sealed tightly with a clipper and used within 24 hours.

9 (S)AE REPORTING

As a market research assessment, this study aims to evaluate a product that is compositionally and nutritionally comparable to existing commercial products and so is close to commercial production and launch. Therefore, it is unlikely that any Adverse Event (AE) may occur during or after the research assessment. However, any clinical event that is judged to be an AE and considered to be related to the product should be reported immediately by the participant and/or carer to the Lead Dietitian. The Lead Dietitian will in turn notify the sponsor, NeoteriQ Ltd. The following parameters will be assessed on a daily basis whilst subjects are taking EasiVits:

- Changes in bowel habits
- Any nausea or vomiting
- Abdominal bloating, distention or pain

If it is noted that any of these symptoms occur whilst taking EasiVits, participants will be asked to contact the Lead Dietitian. Participants will be free to withdraw from the research at any time without if affecting their care. The study product will be submitted to ACBS for approval as a food for Special Medical Purposes (FSMP) available for prescription in the UK.

Participants will be free to withdraw from the research study at any time without it affecting their

care.

9.1 Definitions

An ***adverse event*** is any untoward medical deviation from baseline health occurring to a subject during a clinical trial after signing informed consent, whether or not considered related to the investigational product. Adverse events will be recorded on the standard AE form.

A ***serious adverse event*** is an untoward occurrence that: -

- Results in death or is life threatening
- Results in persistent or significant disability or incapacity
- Requires inpatient hospitalisation or prolongation of existing hospitalisation
- Consists of a congenital anomaly or birth defect
- Is otherwise considered medically significant by the Lead Dietitian

9.2 (Serious) Adverse Events handling

i. Recording of (S)AEs

Any clinical study event that is judged to be an (S)AE, either reported spontaneously by the subject or observed by the Lead Dietitian or his staff, will be recorded on the CRF and on the (S)AE reporting form during the course of the study. The Lead Dietitian will ensure that this information, including onset, duration and nature of event, severity, and action taken, is captured.

ii. Expedited SAE reporting

All SAEs considered potentially related to the use of the study product, must be reported to the chief Lead Dietitian and to the Sponsor by the Lead Dietitian by faxing the completed SAE form within 24 hours. The Chief Lead Dietitian/Sponsor will report these SAEs to the accredited REC that approved the protocol, according to the requirements of that REC.

9.3 Follow-up of adverse events

All (S)AEs considered potentially related to the use of the study product will be followed by the Lead Dietitian until they have abated, or until a stable situation has been reached. Depending on the event, follow up may require additional tests or medical procedures as indicated, and/or referral to the general physician or a medical specialist.

10 STATISTICS

10.1 Sample size calculation

This study is an observational study, and its primary aim is to determine acceptability, and tolerance of the study product. As such, many of the outcome measures are qualitative rather than quantitative. The number of subjects entered into this study is based on a realistic evaluation of the number of subjects likely to be available for recruitment.

10.2 Statistical methods for data analysis

Many of the outcome measures will be qualitative and these will be described in a narrative summarising the study outcomes. Quantitative outcome measures will be summarised, and descriptive statistics of the data will be presented.

11 ETHICAL ASPECTS

11.1 Basic principles and legal situation

As this research involves collecting patient data, the Lead Dietitian will ensure that it is conducted in full conformance with the principles of the 'Declaration of Helsinki' (59th WMA General Assembly, Seoul, October 2008), Good Clinical Practice guidelines as appropriate to nutritional products, and with local legislation of the country in which the research is conducted, whichever affords the greater protection to the individual.

11.2 Ethics Committee

This is a research study on a product that is compositionally comparable to similar vitamin and mineral supplements currently on the UK market and available on prescription through ACBS for IEM. The study protocol and any accompanying material, (e.g. information and informed consent sheets), will be submitted to the local Ethics Committee by the investigator and approval from the

Ethics Committee and the local R&D department obtained in writing before commencing the study - specifying the date on which the Ethics Committee met and granted the approval and specifying version and date of all submitted documents. The investigator will submit a report at least annually to the Ethics Committee that approved the protocol.

11.3 Informed Consent

Prior to research enrolment, written informed consent must be obtained from each subject from the age of 16 years or their legal representative. It is the responsibility of the study team to obtain this written informed consent, after adequate explanation to the subject of the aims, methods, objectives and potential undesirable effects of the research study. Written informed consent should be obtained with the understanding that consent may be withdrawn at any time without prejudice. If appropriate to their level of understanding, an assent form can be signed by the participant up to the age of 15 years in addition to the consent form by their parent/caregiver. Any subject who turns 16 years of age during the study period will be asked to re-consent.

11.4 Confidentiality of study data and Data Protection

NeoteriQ Ltd. and the Lead Dietitian are responsible for ensuring that subject information is treated as confidential and will not be publicly available. All participant records completed during the trial will be identified only by the identification number to maintain participant confidentiality. All participant records must be kept in a locked file cabinet; identification codes lists linking the participant names to participant identification number must be stored separately in a locked file cabinet. Medical records and research records may be looked at and/or copied for research or regulatory purposes by the sponsor, government agencies and authorities as appropriate, provided that participant confidentiality is protected.

Procedures for handling, processing, storage and destruction of data will be compliant with the data protection act 2018 (GDPR). For the purpose of the study and subject to the Participant's consent, the investigational site and the Sponsor shall treat the personal data of the Participants as independent controllers according to the definition of Article 4.7 and the content of Article 24 GDPR.

11.5 Potential risks and benefits of the study

Potential Benefits:

Existing vitamin and mineral supplements for IEM are restricted to one flavour or contain high amounts of added carbohydrate. Conversely, EasiVits contain no added carbohydrate and is unflavoured, allowing patients to add their preferred flavours in order to improve adherence and prevent taste fatigue.

Potential Risks:

Potential risks of the study may include subject refusal to take the products or gastrointestinal symptoms resulting in loss of metabolic control. However, this risk will be minimised as the patient will be monitored clinically. If a subject refuses to take the products for 24 hours, they will return to their normal vitamin and mineral supplement (i.e. the one used before entering the study) to ensure no harm is done to the child. In the case of an adverse event resulting in loss of metabolic control or severe symptoms (e.g. vomiting, rash), whether potentially related to the study product or not, patients would be instructed to call the emergency IMD doctors and dietitian and to go to their local hospital emergency department if they were worried about the severity of symptoms, as is usual practice.

EasiVits are compositionally similar to existing vitamin and mineral supplements. Occasionally, different supplements may cause abdominal pain, vomiting or diarrhea particularly if not taken with sufficient fluid. If there are any problems with tolerance children can stop the research at any time on request of parents/caregivers or health care professionals or at the Lead Dietitians discretion.

11.6 Study closure

The end of the study is defined as the date of the last participant´s last visit plus an additional 3 months for data analysis. The sponsor will complete an end of the study form to notify the REC.

12 MISCELLANEOUS

12.1 Record keeping

Study documents should not be destroyed without prior written agreement between the sponsor and the Lead Dietitian. Should the Lead Dietitian wish to assign study documents to another party, or move them to another location, the sponsor will be notified first.

12.2 Criteria for termination of the trial

The term “Early Termination” refers to a subject’s non-completion of a study, whether by the subject, parent/caregiver, the Lead Dietitian’s decision, or due to discontinuation of the study by the Sponsor.

Subjects may be removed from the study for any of the following reasons:

- A subject’s parent/caregiver requests discontinuation
- The Lead Dietitian initiates removal for medical reasons (i.e. occurrence of any adverse event or condition that could, in the Lead Dietitian’s opinion, interfere with the evaluation of the treatment effect or put the subject at undue risk)
- Protocol non-compliance

Should a subject decide to withdraw, all efforts will be made to complete and report observations as thoroughly as possible. In the event that a subject is withdrawn from the study, the reason for the withdrawal will be documented.

The primary reason for a subject withdrawing prematurely should be selected from the following standard categories:

Adverse Event - events that in the judgment of the Lead Dietitian, for the best interest of the subject, require discontinuation of study product (includes all categories of study product relatedness: Not Related, Unlikely, Possible, Probable, and Definite).

Death - death of the subject

Withdrawal of Consent - subject (parent/caregiver or legal guardian) desires to withdraw from further participation in the study.

Protocol Violation - the subject did not adhere to the protocol requirements (e.g. did not adhere to feeding requirements).

Other - causes of premature termination from the study other than the above, such as theft or loss of study products, termination of study by Sponsor, etc.

12.3 Compensation for subjects

Patients will receive the trial product free of charge. Reimbursement will be offered to the participant or parent/carer for any travel expenses incurred related to the study.

13 REFERENCES

Robert M, Rocha JC, van Rijn M, Ahring K, Belanger-Quintana A, MacDonald A, et al. Micronutrient status in phenylketonuria. Mol Genet Metab. 2013;110 Suppl:S6-17.

Daly A, Evans S, Chahal S, Surplice I, Vijay S, Santra S, MacDonald A. The challenges of vitamin and mineral supplementation in children with inherited metabolic disorders: a prospective trial. J Hum Nutr Diet. 2016 Aug;29(4):434-40. doi: 10.1111/jhn.12354. Epub 2016 Jan 18. PMID: 26781762.

Daly A, Evans S, Gerrard A, Santra S, Vijay S, MacDonald A. The Nutritional Intake of Patients with Organic Acidaemias on Enteral Tube Feeding: Can We Do Better? JIMD Rep. 2016;28:29-39. doi: 10.1007/8904_2015_443. Epub 2015 Oct 29. PMID: 26510853; PMCID: PMC5059221.

Evans, S., Singh, R., Ahring, K., Ashmore, C., Daly, A., Ford, S., Gama, M., Gizewska, M., Hill, M., Ilgaz, F., Newby, C., Pinto, A., Tosi, M., Yimaz Nas, O., Zuvadelli J., MacDonald, A. Global use of casein glycomacropeptide protein substitutes for phenylketonuria (PKU): health professional perspectives. *Nutrients* (submitted for publication)

Brantley, K.D., Douglas, T.D. & Singh, R.H. One-year follow-up of B vitamin and Iron status in patients with phenylketonuria provided tetrahydrobiopterin (BH4). *Orphanet J Rare Dis***13**, 192 (2018). https://doi.org/10.1186/s13023-018-0923-2

Thiele AG, Weigel JF, Ziesch B, Rohde C, Mütze U, Ceglarek U, Thiery J, Müller AS, Kiess W, Beblo S. Nutritional Changes and Micronutrient Supply in Patients with Phenylketonuria Under Therapy with Tetrahydrobiopterin (BH(4)). JIMD Rep. 2013;9:31-40. doi: 10.1007/8904_2012_176. Epub 2012 Oct 17. PMID: 23430545; PMCID: PMC3565664.

14 Appendix 1:

Product Specification

EasiVits UNO

Ingredients:

Calcium phosphate, Inulin, Magnesium phosphate, Choline bitartrate, Calcium carbonate, Vitamin C (Ascorbic acid), Ferric pyrophosphate, Zinc sulphate, Vitamin E acetate, Vitamin B3 (Nicotinamide), Maltodextrin, Vitamin B5 (Calcium d-pantothenate), Vitamin B6 (Pyridoxine hydrochloride), Vitamin B1 (Thiamine hydrochloride), Vitamin B2 (Riboflavin), Copper sulphate, Xanthan Gum, Manganese sulphate, Vitamin A (Retinyl acetate), Folic acid, Potassium iodide, Sodium selenite, Vitamin D3 (Cholecalciferol), D-Biotin, Vitamin K1 (Phylloquinone), Chromium chloride, Sodium molybdate, Vitamin B12 (Cyanocobalamin).

		Per 3g Sachet	**Per 100g**
Energy	kJ	11	367
	kcal	2.7	89
Carbohydrates	g	0.10	3.46
of which sugars	g	0.01	0.31
Protein	g	0.0	0.0
Fat	g	0.00	0.07
Of which saturates	g	0.00	0.07
Fibre	g	0.64	21.4
Salt	g	Trace	Trace

Vitamin A	ug	450	15000
Vitamin D	ug	15	500
Vitamin E	mg	6	200
Vitamin K	ug	12.6	420
Vitamin C	mg	50	1667
Vitamin B1	mg	0.5	17
Vitamin B2	mg	0.6	20
Niacin	mg	8	267

Vitamin B6	mg	0.7	23
Folic Acid	ug	90	3000
Vitamin B12	ug	1.3	43
Biotin	ug	15	500
Pantothenic Acid	ug	3	100
Sodium	mg	0.01	0.41
	mmol	Trace	0.02
Potassium	mg	Trace	Trace
	mmol	Trace	Trace
Chloride	mg	Trace	Trace
	mmol	Trace	Trace
Calcium	mg	400	13333
	mmol	10	332
Phosphorus	mg	280	9333
	mmol	9	301
Magnesium	mg	85	2833
	mmol	3.5	117
Iron	mg	7	233
Zinc	mg	5	167
Copper	mg	0.55	18
Manganese	mg	0.2	7
Selenium	ug	20	667
Chromium	ug	10	333
Molybdenum	ug	10	333
Iodine	ug	70	2333
Choline	mg	180	6000

EasiVits DUO

Ingredients:

Magnesium phosphate, Calcium phosphate, Choline bitartrate, Inulin, Calcium carbonate, Vitamin C (Ascorbic acid), Ferric pyrophosphate, Zinc sulphate, Vitamin E acetate, Vitamin B3 (Nicotinamide), Maltodextrin, Vitamin B5 (Calcium d-pantothenate), Vitamin B6 (Pyridoxine hydrochloride), Vitamin B1 (Thiamine hydrochloride), Vitamin B2 (Riboflavin), Manganese sulphate, Copper sulphate, Xanthan Gum, Vitamin A (Retinyl acetate), Folic acid, Potassium iodide, Sodium selenite, D-Biotin, Vitamin K1 (Phylloquinone), Sodium molybdate, Vitamin D3 (Cholecalciferol), Chromium chloride, Vitamin B12 (Cyanocobalamin).

		Per 5g Sachet	**Per 100g**
Energy	kJ	14	279
	kcal	3.4	67
Carbohydrates	g	0.27	5.4
of which sugars	g	0.01	0.28
Protein	g	0.0	0.0
Fat	g	0.0	0.05
Of which saturates	g	0.0	0.05
Fibre	g	0.5	10
Salt	g	Trace	Trace

Vitamin A	ug	500	10000
Vitamin D	ug	15	300
Vitamin E	mg	9	180
Vitamin K	ug	47	940
Vitamin C	mg	50	1000
Vitamin B1	mg	1	20
Vitamin B2	mg	1.2	24
Niacin	mg	13	260
Vitamin B6	mg	1.2	24
Folic Acid	ug	200	4000
Vitamin B12	ug	2.8	56
Biotin	ug	100	2000
Pantothenic Acid	ug	4	80
Sodium	mg	0.03	0.62

	mmol	Trace	0.03
Potassium	mg	Trace	Trace
	mmol	Trace	Trace
Chloride	mg	Trace	Trace
	mmol	Trace	Trace
Calcium	mg	720	14400
	mmol	18	360
Phosphorus	mg	555	11100
	mmol	17.9	358
Magnesium	mg	215	4300
	mmol	8.8	177
Iron	mg	10.6	212
Zinc	mg	8	160
Copper	mg	0.9	18
Manganese	mg	1	20
Selenium	ug	50	1000
Chromium	ug	18	360
Molybdenum	ug	37	740
Iodine	ug	110	2200
Choline	mg	250	5000